CLAIMS

What is claimed is:

1. A synthetic inhibitor of HAUSP protein binding, the inhibitor having a polypeptide portion that includes the sequence

$$P^1 - Gly - P^3 - Ser,$$

wherein P^1 is one of a Glu residue and an amino acid residue having a side chain that includes a non-polar portion and wherein P^3 is one of a Gly residue and an amino acid residue having a side chain that includes a non-polar portion.

2. The inhibitor of claim 1, wherein P^1 is one of a Glu residue and an amino acid residue having a non-polar side chain.

3. The inhibitor of claim 1, wherein P^1 is selected from the group consisting of a Glu residue, a Pro residue, and an Ala residue.

4. The inhibitor of claim 1, wherein P^3 is one of a Gly residue and an amino acid residue having a non-polar side chain.

5. The inhibitor of claim 1, wherein P^3 is selected from the group consisting of a Gly residue, a Pro residue, and a Val residue.

6. The inhibitor of claim 1, being a polypeptide.

7. The inhibitor of claim 6, wherein the polypeptide includes at least four amino acid residues.

8. The inhibitor of claim 6, wherein the polypeptide includes not more than ten amino acid residues.

9. The inhibitor of claim 1, wherein the polypeptide portion has an amino acid sequence that includes residues 359-368 of human p53 protein.

10. The inhibitor of claim 1, wherein the polypeptide portion has an amino acid sequence that includes residues 441-450 of Epstein-Barr virus nuclear antigen 1 (EBNA1) protein.

11. The inhibitor of claim 1, wherein the polypeptide portion has an amino acid sequence that includes residues 444-447 of EBNA1 protein.

12. The inhibitor of claim 1, wherein the polypeptide portion has an amino acid sequence that includes residues 223-232 of human MDM2 protein.

13 The inhibitor of claim 1, wherein the polypeptide portion has an amino acid sequence that includes residues 226-229 of human MDM2 protein.

14. The inhibitor of claim 1, comprising a moiety that inhibits binding between HAUSP and human p53 protein preferentially to binding between HAUSP and human MDM2 protein.

15. The inhibitor of claim 1, wherein the inhibitor inhibits binding between HAUSP and human MDM2 protein preferentially to binding between HAUSP and human p53 protein.

16. A synthetic inhibitor of HAUSP protein binding, the inhibitor comprising a polypeptide that binds with the surface groove of the TRAF-like domain of HAUSP and interacts with the amino acid residues of HAUSP corresponding to the groove in a manner analogous to the manner in which at least one of p53, MDM2, and EBNA1 proteins interact with the residues.

17. A pharmaceutical composition comprising the inhibitor of claim 1.

18. A synthetic inhibitor of HAUSP protein binding, the inhibitor having a polypeptide portion that includes residues 68-196 of human HAUSP protein.

19. The inhibitor of claim 18, wherein the polypeptide portion includes residues 53-208 of human HAUSP protein.

20. The inhibitor of claim 18, being a polypeptide.

21. The inhibitor of claim 18, comprising a moiety that inhibits binding between the inhibitor and human p53 protein preferentially to binding between the inhibitor and human MDM2 protein.

22. A synthetic inhibitor of HAUSP protein binding, the inhibitor having a polypeptide portion that includes residues 68-196 of human HAUSP protein, wherein the identity of at least one of residues 152, 162, 165, and 168 is modified from its naturally-occurring identity.

23. The inhibitor of claim 22 wherein at least one of the following is true:
i) residue 152 is a residue other than Arg;
ii) residue 162 is a residue other than Glu;
iii) residue 165 is a residue other than Trp; and
iv) residue 168 is a residue other than Ser.

24. A synthetic inhibitor of HAUSP protein binding, the inhibitor having a polypeptide portion that includes residues 68-196 of human HAUSP protein, wherein the identity of at least one of residues 164, 165, and 167 is modified from its naturally-occurring identity.

25. The inhibitor of claim 24 wherein at least one of the following is true:
i) residue 164 is a residue other than Asp;
ii) residue 165 is a residue other than Trp; and
iii) residue 167 is a residue other than Phe.

26. A method of inhibiting binding between HAUSP protein and a second protein with which HAUSP protein normally binds, the method comprising contacting the HAUSP protein with a synthetic inhibitor having a polypeptide portion that includes the sequence

P^1 - Gly - P^3 - Ser,

wherein P^1 is one of a Glu residue and an amino acid residue having a side chain that includes a non-polar portion and wherein P^3 is one of a Gly residue and an amino acid residue having a side chain that includes a non-polar portion.

27. A method of inhibiting binding between HAUSP protein and a second protein with which HAUSP protein normally binds, the method comprising contacting the HAUSP protein with a synthetic inhibitor having a polypeptide portion that includes residues 359-368 of human p53 protein.

28. A method of inhibiting binding between HAUSP protein and a second protein with which HAUSP protein normally binds, the method comprising contacting the HAUSP protein with a synthetic inhibitor having a polypeptide portion that includes residues 441-450 of EBNA1 protein.

29. A method of inhibiting binding between HAUSP protein and a second protein with which HAUSP protein normally binds, the method comprising contacting the HAUSP protein with a synthetic inhibitor having a polypeptide portion that includes residues 223-232 of human MDM2 protein.

30. A method of inhibiting binding between HAUSP protein and a second protein with which HAUSP protein normally binds, the method comprising contacting the second protein with a synthetic inhibitor having a polypeptide portion that includes residues 53-196 of human HAUSP protein.

31. A method of inhibiting survival of a human cell, the method comprising contacting the cell with a synthetic inhibitor having a polypeptide portion that includes the sequence

P^1 - Gly - P^3 - Ser,

wherein P^1 is one of a Glu residue and an amino acid residue having a side chain that includes a non-polar portion and wherein P^3 is one of a Gly residue and an amino acid residue having a side chain that includes a non-polar portion.

32. The method of claim 31, wherein the polypeptide portion has an amino acid sequence that includes residues 359-368 of human p53 protein.

33. The method of claim 31, wherein the polypeptide portion has an amino acid sequence that includes residues 441-450 of EBNA1 protein.

34. The method of claim 31, wherein the polypeptide portion has an amino acid sequence that includes residues 223-232 of human MDM2 protein.

35. The method of claim 31, wherein the cell is a cancer cell.

36. A method of enhancing survival of a human cell, the method comprising contacting the cell with a synthetic inhibitor having a polypeptide portion that includes residues 53-196 of human HAUSP protein.

37. The method of claim 36, wherein the inhibitor exhibits greater binding affinity for human MDM2 protein than for human p53 protein.

38. The method of claim 36, wherein the identity of at least one of HAUSP residues 164, 165, and 167 is modified from its naturally-occurring identity.

39. The inhibitor of claim 38, wherein at least one of the following is true:
i) residue 164 is a residue other than Asp;
ii) residue 165 is a residue other than Trp; and
iii) residue 167 is a residue other than Phe.

40. A method of assessing the ability of a compound to inhibit interaction between HAUSP protein and a second protein with which HAUSP protein normally interacts, the method comprising

covalently linking the compound with a portion of HAUSP protein that includes residues 53-196 of human HAUSP protein to form a linked product,

crystallizing the linked product, and

assessing the crystal structure of the crystallized linked product,

whereby interference of the compound portion of the linked product with a region of the HAUSP protein portion of the linked product with which the second protein normally binds indicates that the compound can inhibit binding between HAUSP protein and the second protein.

41. The method of claim 40, wherein compound is linked with the portion of HAUSP protein by way of a polypeptide linker.

42. The method of claim 40, wherein compound is linked with the portion of HAUSP protein by way of a sterically flexible linker.

43. A crystallizable product for assessing binding of a compound with HAUSP protein, the product comprising a first polypeptide portion including residues 53-196 of human HAUSP protein linked with the compound by way of a sterically flexible linker.

44. The product of claim 43, wherein the compound is a polypeptide.

45. The product of claim 43, wherein the compound is a domain of a protein known to interact with HAUSP protein.

46. A synthetic inhibitor of HAUSP-ubiquitin interaction, the inhibitor comprising a polypeptide, wherein the inhibitor binds the observed surface cleft on the isopeptidase domain (between the Thumb and the Palm) of HAUSP and wherein the inhibitor make similar interactions to surrounding amino acids of HAUSP as does the C-terminal peptide of ubiquitin.

47. The inhibitor of claim 46, containing the sequence P^4-P^5-P^6, wherein P^4 is Leu, Ile, Met, Val, or Phe; P^5 is Arg, Lys, or His; and P^6 is Leu, Ile, Met, Val, or Phe.